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EXAMINER	
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1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,644	OHTA ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1, 3-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims. Claims 1-16 are pending. Applicant's election with traverse of Group III, claims 2, 12-16, drawn to a method of antibody production, in Applicants reply filed on 11-16-2007 is acknowledged.

Response to arguments

On page 7 of Applicants' Response to the Restriction Requirements, Applicants argue that the technical feature of the present claims do define a contribution over Sale et al., (2001, Nature, pp. 921-926) because Sale discloses hypermutation as a mechanism to generate antibody diversity whereas the instant claims are drawn to a mechanism of homologous recombination to produce diverse antibodies. Moreover, Applicants contend that "hypermutation and homologous recombination are mechanistically different methods for introducing mutations". Additionally, Applicants argue that "If the restriction requirement is not withdrawn in its entirety, then it should at least be modified to allow prosecution in this application of at least claims in Invention Groups III and IV. Inventions of Groups III and IV are directed to a method for antibody production and the antibody produced by said method, respectively. Applicants state, "Thus examining the claims of Invention Groups III and IV can be madde without serious burden". Such is not persuasive.

As stated in the previous office action, methods for the generation of diverse antibodies by immunocytes have been described in the Sale reference by teaching generation of antibodies by hypermutation in the in the V domain of the light chain locus. Moreover, the art teaches the generation of antibody diversity by homologous recombination at the antibody locus in species

such as chickens, rabbits, cattle, and pigs (See Arakawa et al., Science, 2002, p. 1301-1306, paragraph below). Moreover, as indicated in MPEP 1850, PCT Rule 13.2, as it was modified effective July 1, 1992, no longer specifies the combinations of categories of invention which are considered to have unity of invention. The categories of invention in former PCT Rule 13.2 have been replaced with a statement describing the method for determining whether the requirement of unity of invention is satisfied. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more special technical features. In the instant case, the special technical feature shared by the Groups is anticipated by the prior art of Sale et al., (Nature, August 2001, pp. 921-926).

In relation to the rejoining of elected Groups III, drawn to a process ,and Group IV, drawn to the product resulting from the process, it is noted that the MPEP 1893.03(d) states: If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. Any nonelected product claim that requires all the limitations of an allowable product claim, and any nonelected process claim that requires all the limitations of an allowable process claim, should be rejoined. See MPEP § 821.04 and § 821.04(a). Any nonelected processes of making and/or using an allowable product should be considered for rejoinder following the practice set forth in MPEP § 821.04(b).

Therefore, claims 1 and 3-11, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention pursuant to 37 CFR 1.142(b), there being no allowable generic or linking claim.

The restriction is considered proper and made FINAL.

Claims 2 and 12-16 are currently under examination to which the following grounds of rejection are applicable.

Specification Objection

The disclosure is objected to because of the following informalities:

At page 11, lines 5-7, the sentence reciting "but it is known that actually functional in antibody production is VJ rearranged one" is grammatically incorrect. Appropriate correction is required.

At page 5, line 21, the speciation recites the abbreviation "TSA". An abbreviation should be spelled out at its first encounter.

Information Disclosure Statement

1. The information disclosure statements filed on 08-02-2007, 06-06-2005, 03-23-2005, 01-26-2005, 01-09-2007 and 06-27-2006 have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

2. The information disclosure statement filed on 08-02-2007 and 01-09-2007 fail to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each

publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The following references were not considered for the reasons described below:

> Reference 1 of 08-02-2007 is incomplete in the absence of a publication,
> Reference CA of 01-09-2007 is incomplete in the absence of an english abstract or translation.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

. Claim 16 recites the limitation "said antigen" in the preamble of the claim. There is insufficient antecedent basis for this limitation in the claim. The metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 112, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing antibodies comprising enhancing

DNA homologous recombination at an antibody locus wherein DNA homologous recombination is occurring at said locus using the chicken DT40 B-cell line by relaxing the chromatin structure of chromosomes with trichostatin in said immunocytes, and thereby obtaining diverse antibodies,

does not reasonably provide enablement for a method of producing antibodies comprising enhancing DNA homologous recombination at an antibody locus e.g., Ig , in any immunocyte cell line other than in the chicken DT40 B-cell by relaxing the chromatin structure with trichostatin. The specification teaches the generation of diverse IgM on cell membranes of the chicken B-lymphocyte line, DT40, from clones that did not express IgM on their surfaces after incubation with trichostatin A (TSA) which inhibits histone deacetylase and thus promotes H4 acetylation. Moreover, DT40 cells were transfected with plasmid #18-4 comprising a probe in the constant region of the light chain locus used for Southern Hybridization to detect immunoglobulin light chain (IgLC) transcripts in isolated DNA of transfected DT40 nuclei.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims, when given the broadest possible interpretation, encompass a method for producing diverse antibodies in immunocytes of different eukaryotic species, wherein first assembly of the antigen receptor genes from different V, D and J segments by site specific V(D)J recombination in an antibody locus is followed by either B cell hypermutation e.g., somatic mutation or pseudogene template homologous recombination e.g., gene conversion. The word immunocytes is not defined in the as-filed specification and is broadly interpreted as any cell that can mediate phagocytosis in stress response and/or inflammation and produces antibodies. Therefore, the claims broadly encompass immunocytes of different species wherein with antibody diversity is not necessarily the result of homologous recombination. Furthermore, it was well known at the time of filing that only B cells are capable of rearranging the Ig locus. The specification provides insufficient data to enable claims directed to the method as broadly claimed. Thereby, specific issues including frequency and nature of non-reciprocal homologous recombination whereby modifications in an acceptor gene are copied form a homologous donor sequence, e.g., template modification, have to be examined and considered for patentability regarding the broadly claimed methods of producing antibodies by enhancing homologous recombination after relaxing the chromatin structure at an antibody locus site.

The as filed specification teaches the generation of diverse IgM on cell membranes of the chicken B-lymphocyte line, DT40, cell line (e.g., 3H12) (p. 11, lines 15-25). DT40 cells were transfected with plasmid #18-4 comprising a probe in the IgLC locus said probe used for Southern Hybridization to detect IgLC transcripts from isolated DNA. The specification discloses that transfected 10^7-10^8 DT40 cell were cultured for 8 hr in a medium with different concentration of TSA and the DNA recovered from nuclei was used for Southern Blot analysis.

Results confirmed that cell lines were relaxed by TSA and thus the VJ region of the light chain locus was more accessible for digestion with MNase (p. 13, lines 10-18). Additionally, the specification teaches that single colonies of DT40 cells that did not expressed IgM were incubated with TSA for three weeks at and the presence of IgM was detected by FACS after binding to a FITC-labeled anti chicken IgM antibody (p. 15, lines 15-35) . However, the specification only teaches detection of IgM in TSA-treated DT40 cells. Moreover, the specification is silent about the demonstration of the presence or the nature of a non-specific recombination event e.g., events resulting from a single gene conversion instead of independent homologous recombination events. Indeed Applicants state "It is thought that the IgM (+) cells were generated as a result of IgM(-) cells undergoing homologous recombination" (p. 15, lines 33-34). The specification further fails to disclose adequate description of other hosts immunocytes that may be utilized in the instant recombination methods.

At the time of filing, it was well known in the art that DT40s were convenient models for making gene-targeted mutants. For example, Sonoda et al., *(Phil. Trans. R. Lond.* 356,111-117) teaches that DT40 is an avian leucosis virus-transformed chicken B-lymphocyte line which exhibits high ratios of targeted to random integration of transfected DNA constructs. Moreover, Sonoda et al., discloses that most transfected DNA integrates into the genome at random chromosomal locations with the unique exception of chicken B-lymphocyte lines, exhibiting targeting efficiencies that are orders of magnitude higher that those observed in mammalian cells, clearly supporting the notion that efficient somatic homologous recombination is intrinsic to primary chicken B lymphocytes (p. 111, col. 1 and 2). Moreover, targeting efficiency affected to the extent of homology between the targeting vector and the target locus in most cells, does

not affect homologous recombination or Ig gene conversion in chicken B lymphocytes, while it affect efficient recombination in other immunocytes (p. 111, col. 2). In addition the author teaches that the phenotype of wild type DT40 is highly stable allowing for tracking of abnormal phenotypes due to gene targeted clones to mutation of the genes rather that clonal variation of the wild type phenotype (p. 112, col. 1, paragpah1). These observations are critical as Applicants have used DT40 as host immunocytes for the homologous recombination resulting in the production of diverse antibodies.

In so far as enhancing DNA recombination at the Ig locus, the art discloses that only B cells exhibit V(D)J recombination. B cells then further modify the rearranged V segments by either untemplated hypermutation or pseudogene templated gene conversion (Arakawa et al., Science, 2002, p. 1301-1306). Arakawa et al., (2002, Science) discloses that species such as sheep exclusively use somatic hypermutation for V segment diversification, whereas others such as chickens, rabbits, cattle, and pigs rely predominantly on Ig gene conversion to further modify the rearranged V segments (p. 1301). Indeed, Weill et al., (1996, Immunology Today pp. 1-6) discloses successive homologous recombination in the chicken and rabbit Ig loci to carry the potential diversity necessary for the generation of their protective B-cell immune repertoire. Gene conversion by successive homologous recombination is necessary in species that only have a single or several functional V genes. Hence, successive events of homologous recombination using upstream donor functional and non functional pseudo V genes in chickens, rabbits, (Weill et al., p, 3, columns 1 and 2) cattle, and pigs generates antibody diversity. This is in contrast with antibody diversity in B-cell of other species including rodents and human B-cells wherein antibody diversity is generated by a single homologous recombinant event by rearrangement of

antibody light chain genes, i.e., a single V to a single J, or rearrangement of the heavy chain genes i.e., a single D to a single J and then a single V to the fused D-J segment (Watson et al., (2001, Recombinant DNA, pp. 295-298). The instant claims embrace immunocytes from a wide range of host mice, primate, sheep, cows, avian, horses, rhesus monkeys in terms of their mechanisms to achieve antibody diversity. The art teaches that only B-cell recombine the Ig locus. Moreover, the art discloses that only a few species diversify the B-cell immune repertoire by successive rounds of homologous recombination. Therefore, it would require undue experimentation for the skilled artisan to generate enhanced recombination at an antibody locus in numerous host immunocytes since only B-cells exhibit recombination of the Ig locus. Moreover, it would require further experimentation to demonstrate the ability to enhance homologous recombination by relaxing the chromatin structure in lymphocytes of a genus of species as claimed as many species do not generate antibody diversity by enhancing homologous recombination of the rearranged V segments after B-cells first assemble their antigen receptor genes V, D, and J but rather by initial site specific V(D)J recombination in an antibody locus. The instant claims embrace not only chicken DT40B lymphocyte, but a genus of eukaryotic immunocytes, that would need to be studied and tested for their homologous recombination abilities. In relation to relaxing the chromatin structure, the claims embrace any number of ways of induction of chromatin changes in a cell e.g., deacetylase inhibitors, chromatin remodeling machinery inhibitors. The specification discloses at page 5, lines 1-5, that trichostatin, a deacetylase inhibitor, is added to the DT40 cells to relax the chromatin to induce an open chromatin configuration and/or gene expression at the target locus before genetic targeting. No other mechanisms of relaxing the chromatin are disclosed. Therefore, molecular mechanisms of

inducing antibody diversification would have to be studied and tested to make and definitively show that one of skill in the art is enable for the generation of said diversification by homologous recombination in any immunocyte and of a wide number of different species in terms of their requirements to generate antibody diversity, by relaxing the chromatin structure under any condition. .

Hence it would require undue experimentation for the skilled artisan to make and use the invention as claimed. As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to extensively test the molecular bases for enhancing homologous recombination at an Ig locus to generate antibody diversity in numerous host immunocytes, and species as claimed. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) in view of McMurry et al., (2000, Science 495-498) and further in view of Watson et al., (2001, Recombinant DNA, pp. 297-304).

Sonoda et al., teaches the use of chicken B-lymphocyte line DT40 for the production of diverse antibodies. Moreover, Sonoda et al., discloses that efficient homologous recombination is an intrinsic characteristic of primary chicken B lymphocytes (p.111, col. 2). Further, B-lymphocye line DT40 exhibit Ig conversion by nucleotide sequence blocks derived from V region pseudogenes that are transferred to functional rearranged V(D)J segments. The teachings clearly indicate that B-lymphocyte line DT40 undergo rearrangement of antibody chains by homologous recombination of the chicken Ig loci to generate diversity (p. 111, col.2).

Sonoda et al., does not specifically teach enhancing homologous recombination by relaxing the chromatin.

However, at the time the invention was made, McMurry et al., discloses a role for histone acetylation in the developmental regulation of V(D)J recombination. Specifically, McMurry et al., discloses that diversity in the V(D)J rearrangement of the T cell receptor depends on accessibility of said V(D)J locus to the recombinase activating enzyme (p. 495, col. 1 and 2).

Moreover, McMurry et al., teaches a model for V(D)J recombination by inducing the region- and developmental stage-specific hyperacetylation of histone H3 which directs accessibility of acetylating enzymes to the V(D)J locus.

Sonoda and McMurry et al., do not specifically disclose that regulation of V(D)J recombination is the same in T cells and immunocytes producing antibodies.

However, at the time the invention was made it was well known in the art as exemplified by the teachings of Watson that recombination of the V, D, J and C segments in T cell receptor genes is similar to the recombination of the antibody V(D)J genes (pp. 303-304).

Therefore, in view of the benefits of using a B-lymphocye line DT40 for the production of diverse antibodies by enhancing homologous recombination as taught by Sonoda, it would have been *prima facie* obvious for one of skill in the art to enhance the accessibility of the recombinant activating enzyme to the V(D)J locus by relaxing the chromatin structure of chromosomes in the DT40 B-lymphocytes, particularly because McMurry demonstrates that direct access of acetylating enzymes to the V(D)J locus in the T receptor gene regulates V(D)J recombination. Moreover, it would have been *prima facie* obvious for one of skill in the art that if acetylation of histone provides accessibility of recombinase activating enzyme to the V(D)J locus in a T cell, it would also provide accessibility to the V(D)J locus in an antibody producing immunocyte, as the molecular bases of genetic diversity for the V(D)J locus are similar in both T and B cells. The manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art at the time the invention was made would had been motivated to combine the Sonoda, McMurry and Watson references with a reasonable expectation of success, particularly to

improve the production of antibodies by homologous recombination by allowing accessibility of recombinant enzymes to regulate V(D)J recombination.

Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) in view of McMurry et al., (2000, Science 495-498) and further in view of Watson et al., (2001, Recombinant DNA, pp. 297-304) as applied to claims 1 and 15 above and further in view of Choy et al., (Mol Cell Biol. 2002, pp 8215-8225) .

The teachings of Sonoda, McMurry and Watson are outlined in the paragraph above. Sonoda, McMurry and Watson do not teach the histone deacetylase inhibitor, trichostatin A.

However, at the time the invention was made, Choy et al., teaches that transcription requires acetylation of histone N-terminal tails to promote an open chromatin conformation. Additionally, a similar role for histone acetylation is found during chromosomal replication. Moreover Choy et al., discloses that restoring H4 acetylation with the histone deacetylase inhibitor trichostatin A (e.g., 30 μg of TSA/ml overnight) promotes checkpoint recovery and thus maintain genomic integrity during chromosomal replication (p. 8224, col. 1 and 2).

Therefore, in view of the benefits of using a B-lymphocye line DT40 for the production of diverse antibodies by enhancing homologous recombination as taught by Sonoda, it would have been *prima facie* obvious for one of skill in the art enhance the accessibility of the recombinant activating enzyme to the V(D)J locus by relaxing the chromatin structure of chromosomes in the DT40, particularly because McMurry demonstrates that direct access of

acetylating enzymes to the V(D)J locus in the T receptor gene regulates V(D)J recombination. Moreover, it would have been *prima facie* obvious for one of skill in the art that if acetylation of histone provides accessibility of recombinase activating enzyme to the V(D)J locus in a T cell, it would also provide accessibility to the V(D)J locus in an antibody producing immunocyte as the molecular bases of genetic diversity for the V(D)J locus are similar in both T cell and B cells. Further, it would have been *prima facie* obvious to use the histone deacetylase inhibitor trichostatin A, at different concentrations and at different times, particularly because Choy et al., discloses that acetylation of histone promotes an open chromatin conformation and genomic integrity during replication. Moreover, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 105 USPQ 233. One of ordinary skill in the art at the time the invention was made would had been motivated to combine the Sonoda, McMurry, Watson and Choy references with a reasonable expectation of success, particularly to improve the production of antibodies by homologous recombination by using the histone deacetylase inhibitor trichostatin A to allow acetylation of histone and thus accessibility of recombinant enzymes to regulate V(D)J recombination.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) in view of McMurry et al., (2000, Science 495-498) and further in view of Watson et al., (2001, Recombinant DNA, pp. 297-304) as applied to claims 1 and 15 above and further in view of Sale et al., US Patent 7,122,339, Date of Patent October 17, 2006.

The teachings of Sonoda, McMurry and Watson are outlined in the paragraph above. Sonoda, McMurry and Watson do not teach preparing a target antigen, coating the immunocyte with the target said antigen to select specific antibodies binding said antigen.

However, at the time the invention was made, Sale et al., teaches a method for selection of antibodies from a pool of generated ab that are expressed on the surface of a host cell comprising mixing host cells with antigen-coated magnetic beads in order to specifically select an immunoglobulin of the desired specificity displayed on the surface of the host cell (col. 11, lines 19-24). Moreover, Sale et al., discloses that it is advantageous to culture and establish a plurality of clonal populations to increase the probability of identifying a cell which secretes a gene product having the desired activity (col. 27, lines 32-43; col. 24, lines 8-11).

Therefore, in view of the benefits of using a B-lymphocye line DT40 for the production of diverse antibodies by enhancing homologous recombination as taught by Sonoda, it would have been *prima facie* obvious for one of skill in the art to enhance the accessibility of the recombinant activating enzyme to the V(D)J locus by relaxing the chromatin structure of chromosomes in the DT40, particularly because McMurry demonstrates that direct access of acetylating enzymes to the V(D)J locus in the T receptor gene regulates V(D)J recombination. Moreover, it would have been *prima facie* obvious for one of skill in the art that if acetylation of histone provides accessibility of recombinase activating enzyme to the V(D)J locus in a T cell, it would also provide accessibility to the V(D)J locus in an antibody producing immunocyte as the molecular bases of genetic diversity for the V(D)J locus are similar in both T cell and B cells. Further, it would have been *prima facie* obvious to select the diverse immunocytes by contacting with antigen of interest to isolate and culture selective clones for specific antibody expansion.

One of ordinary skill in the art at the time the invention was made would had been motivated to combine the Sonoda, McMurry, Watson and Sale references with a reasonable expectation of success, particularly to improve the production of antibodies by homologous recombination by allowing accessibility of recombinant enzymes to regulate V(D)J recombination and further mixing the generated immunocytes with antigens to specifically select an immunoglobulin of the desired specificity.

Conclusion

Claims 2 and 12-16 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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